REMARKS/ARGUMENTS

The Invention

The invention is directed to a method of diagnosing cancer in a patient. The method comprises assaying a sample from the patient for the presence of extracellular cAMP-dependent protein kinase (ECPKA), wherein an elevated level of ECPKA in the sample is indicative of cancer in said patient.

The Pending Claims

Claims 1-8 are currently pending, which claims are directed to the above-described method of diagnosing cancer.

The Amendments to the Specification

The paragraphs beginning at page 13, line 24, and page 14, line 26 have been amended to replace internet addresses with the names of the databases or corresponding printed publications referred to by the internet addresses. No new matter has been added by way of these amendments.

The Amendments to the Claims

The claims have been amended to claim more distinctly and point out more particularly the present invention. Claims 3 and 6 have been amended to recite "the activity level of ECPKA." This amendment is supported by the specification, for example, at page 22, lines 11-12. Claim 9 has been cancelled.

Claims 10-20 have been cancelled as being drawn to nonelected subject matter. Applicants reserve the right to pursue any cancelled subject matter in a continuation, continuation-in-part, divisional, or other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter. Accordingly, no new matter has been added by way of these amendments.

The Office Action

The Office makes final the restriction requirement set forth in the prior Office Action dated December 9, 2004. The restriction requirement was modified in view of Applicants arguments.

The Office rejects claims 1-9 under 35 U.S.C. § 112, first paragraph, for alleged non-enablement and lack of written description. The Office also rejections claims 1-9 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Finally, the Office objects to the presence of internet addresses in the specification.

As claim 9 has been cancelled, the foregoing rejections and objections are addressed only insofar as they pertain to claims 1-8. Reconsideration of these rejections and objection is respectfully requested for the reasons discussed below.

Discussion of Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

The Office rejects claims 1-8 under Section 112, first paragraph, as allegedly lacking enablement. In particular, the Office alleges that the claims are not enabled in four respects: (a) as to the use of ECPKA expression levels, (b) as to the use of any type of sample, (c) as to the use with any type of cancer, and (d) as to the specific diagnosis of one type of cancer over another. The rejections are overcome for the reasons discussed below.

A. Enablement as to the Use of ECPKA Expression Levels

The Office recognizes that the claimed method encompasses assaying a sample for the presence of ECPKA according to activity level or expression level, and does not dispute that the claimed method is enabled as to the assay of ECPKA activity. However, the Office Action alleges that the claimed method is not enabled as to the assay of ECPKA expression level because the present application allegedly does not provide any structural characteristic that would allow one to distinguish between ECPKA and PKA proteins. Thus, the Office alleges that there would be no way to determine whether an assayed protein level was due to the presence of ECPKA or PKA.

The Office's reasoning reflects a fundamental misconception of the claimed invention. As explained in the specification, ECPKA is "extracellular" PKA, whereas other forms of PKA are intracellular or are membrane-bound PKA (i.e., "ecto-cellular"). Thus, one can distinguish between ECPKA and PKA expression levels, for example, on the basis of

whether an assay was performed on the extracellular or cellular fraction of a sample (e.g., specification at p. 9, lines 25-30). Furthermore, such an assay can be performed using known antibodies to the "C" catalytic subunit of PKA (e.g., specification at p. 33, Example 7). One can also distinguish between ECPKA and PKA expression levels on the basis of enzyme activity in the presence of cAMP. In this respect, as demonstrated in Cho et al., *Proc. Natl. Acad. Sci. USA*, 97: 835-840 (2000) (copy enclosed), PKA exists in all cells as an inactive holoenzyme, i.e., a C subunit bound with an R subunit. Thus, enzyme activity cannot be measured without addition of the exogenous cAMP, which releases the C subunit to become an active enzyme. In contrast, the ECPKA exists as a C subunit only; therefore, it is active in the absence of exogenous cAMP.

As to the Office's allegation that the specification provides no structural characteristic of ECPKA, such allegation simply is not true. The examples disclose detecting ECPKA using antibodies to the "C" catalytic subunit of PKA (e.g., specification at p. 33, Example 7), thereby disclosing that the catalytic subunit of ECPKA is structurally similar to the known catalytic subunit of PKA. Later-published studies provide further evidence of the disclosed similar structures (see, e.g., Cho et al., *Biochem. Biophys. Res. Commun.*, *278*(3): 679-84 (2000) (copy enclosed)). Indeed, it is on the basis of this similar structure and resulting catalytic activity that one can use PKA activity as a basis to measure the presence of ECPKA in the extracellular matrix. Knowledge of the exact structure of ECPKA, or of the exact structural differences between ECPKA and other forms of PKA, is not required to meet the enablement standard. All that is required is sufficient guidance to allow one of ordinary skill in the art to make and use the claimed invention.

The Office also questions the viability of the claimed method in so far as it involves an assay of ECPKA expression levels because, according to the Office, it is not possible to predict from the disclosure whether increased ECPKA activity is due to increased ECPKA expression as opposed to another mechanism of protein regulation. As support for this proposition, the Office cites studies relating to SRC and CDK4 (not ECPKA or PKA), which disclose that mechanisms exist for enhancing the activity level of these proteins without increasing their expression (e.g., concentration).

However, the Office provides no evidence that the mechanisms by which the activity of SRC and CDK4 can be increased are likely to be involved in ECPKA activity. In the

absence of such evidence, the mechanisms that affect SRC and CDK4 proteins are of little relevance to the ECPKA activity.

Furthermore, studies have shown that PKA expression is enhanced in human cancer cell lines and in primary tumors (e.g., specification at p. 3, lines 10-18), and the Examples of the present application demonstrate that ECPKA expression is regulated by PKA expression (e.g., specification at p. 33, Example 7). Such evidence strongly suggests that the enhanced ECPKA activity is linked to enhanced ECPKA expression, and clearly outweighs the evidence presented by the Office.

For the foregoing reasons, the Office has not met its burden of showing a lack of enablement as to the use of the claimed method in connection with an assay of ECPKA expression levels. Accordingly, the Section 112 rejection in this regard is improper and should be withdrawn.

B. Enablement of Different Sample Types

The Office action contends that one of ordinary skill in the art would not expect to detect ECPKA in all types of samples because R subunit variants have not been detected in certain types of tumors (e.g., renal and CLL tumor cells). As support for this contention, the Office refers to a study by Weber et al., which allegedly discloses that only a "regular" R subunit was found and no variants were detected. The Office thus concludes that no ECPKA would be detected in the context of these types of cancers.

The study reported in Weber et al. involved assaying the whole cell or intracellular fraction of the samples disclosed therein; it did not involve an assay of the extracellular fraction of the samples disclosed therein and, thus, did not test for ECPKA. As disclosed in the specification, ECPKA presents as a free "C" subunit (specification at page 35, lines 2-3). Furthermore, as previously discussed, the "C" subunit of ECPKA is structurally and functionally similar to the C subunit of PKA. Accordingly, an assay of the whole cell or intercellular fraction of a sample, as disclosed in Weber et al., would not distinguish between ECPKA and PKA activity or expression. Thus, Weber et al. does not show an absence of ECPKA in renal cell or CLL cancers.

Furthermore, the Examples of the present application, and additional evidence submitted herewith, demonstrate that ECPKA activity is elevated in a wide variety of cancer cells, including renal cell carcinoma (e.g., specification at p. 34, Table III; Declaration under

37 C.F.R. § 1.132 of Yoon Cho-Chung, M.D., Ph.D., at paragraph 3 (submitted herewith)). Such evidence overcomes the Office's concerns this regard.

The Office also alleges that the specification provides insufficient guidance as to how to employ the claimed method using a solid sample as opposed to a fluid sample. As previously discussed, the claimed method can be practiced by assaying the extracellular fraction of a sample for ECPKA activity. One of ordinary skill would recognize that a solid sample can be used, for example, by fractionating the sample to remove the cellular component, leaving only the extracellular component for testing. Alternatively, a solid sample could be cultured in a medium, and the medium can be tested in the absence of the cells or cellular contents. In this respect, the examples disclose culturing cells in a medium, and testing the medium (without the cells and without lysing the cells) for PKA activity, thereby providing specific guidance.

Thus, the specification enables the use of a solid sample (e.g., a tissue sample) in conjunction with the claimed method. Accordingly, the Section 112 rejection is improper in this regard and should be withdrawn.

C. Enablement as to Different Types of Cancer

The Office further contends that the specification provides insufficient guidance for practicing the claimed method with cancer cell types other than carcinomas. Specifically, the Office doubts that the method of the invention can be used with respect to sarcomas.

Experimental evidence submitted herewith shows an elevated ECPKA activity level is detectable in the extracellular medium of sarcoma cells Declaration under 37 C.F.R. § 1.132 of Yoon Cho-Chung, M.D., Ph.D., at paragraph 3 (submitted herewith)). Thus, based on the disclosure of the specification, one of ordinary skill in the art could practice the claimed method to diagnose both sarcomas and carcinomas without undue experimentation. The Section 112 rejection is, therefore, improper in this regard and should be withdrawn.

D. Enablement as to Diagnosing Specific Cancer Types

The Office alleges that claim 4 is not enabled because it does not recite a specific method step of identifying one of the recited types of cancer. Specifically, the Office contends that the specification does not enable one of ordinary skill in the art to diagnose the cancers recited in the claim.

It is well within the skill of the ordinary artisan to diagnose a particular type of cancer in conjunction with the claimed method. Indeed, the field is rich with various tools and methods that may be employed with the claimed method to determine the specific type of cancer involved (e.g., specification at p. 10, lines 1-16). Furthermore, the Office provides no evidence suggesting that a subsequent step of diagnosing a specific cancer type requires undue experimentation or extraordinary skill. Accordingly, the Office has not met its burden of proof with regard to this allegation.

In view of the foregoing, claims 1-8 are enabled by the disclosure of the subject application. Accordingly, the enablement rejections under Section 112, first paragraph should be withdrawn.

Discussion of Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

The Office rejects claims 1-8 under Section 112, first paragraph, as allegedly lacking written description. In particular, the Office alleges that the specification does not describe ECPKA in a manner consistent with the standards set forth in *University of California v. Eli Lilly and Co.*, 119 F.3d. 1559, 43 U.S.P.Q. 2d. 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d. 1316, 63 U.S.P.Q. 2d. 1609 (Fed. Cir. 2002), because it allegedly describes ECPKA soley by its function, without any description of its structure.

First, the claims are not directed to ECPKA *per se*. Rather, the claims are directed to a method that involves measuring the activity level of a naturally occurring protein. Accordingly, the line of cases cited in support of the written description rejection does not apply to the pending claims.

Furthermore, the specification explicitly discloses the structure of the relevant portions of ECPKA along with the functional aspects of ECPKA associated with such structure. For example, ECPKA is disclosed as existing in the active "free" C subunit form, which "C" subunit is structurally related to the "C" subunit of other forms of PKA, which are known (e.g., specification at p. 35, lines 2-3). This is evidenced by the fact that antibodies to the "C" subunit of PKA can be used to detect the "C" subunit of ECPKA (e.g., specification at Example 7). In addition, the active C subunit of ECPKA uses kemptide for its catalytic activity, a function which no other known kinase possesses, and is potently inhibited by PKI (PKA-specific inhibitor protein) (see Cho et al., *supra*). Moreover, the application discloses a

direct correlation between the similarity in the structure of ECPKA to PKA with a similarity in catalytic function. Accordingly, the application discloses sufficient structure correlated with the function of ECPKA to meet the written description requirement even according to the cases cited by the Office.

In view of the foregoing, the subject matter of claims 1-8 is sufficiently described in the present application so as to convey to one of ordinary skill in the art that Applicant had possession of the claimed invention at the time the subject application was filed. Thus, the written description rejection under Section 112, first paragraph, should be withdrawn.

Discussion of Rejection Under 35 U.S.C. § 112, Second Paragraph

The Office rejects claims 1-8 under Section 112, second paragraph, as allegedly indefinite. In particular, the Office objects to the term "ECPKA" because it is reportedly a "laboratory" designation that is not a unique identifier. Applicants submit that the term "ECPKA" is not a laboratory designation, and is defined in claim 1 as extracellular cAMP-dependent protein kinase. The limitation "extracellular" is sufficient to distinguish the claimed subject matter. Accordingly, the metes and bounds of claims 1-8 are clear, and the Section 112, second paragraph, rejection should be withdrawn.

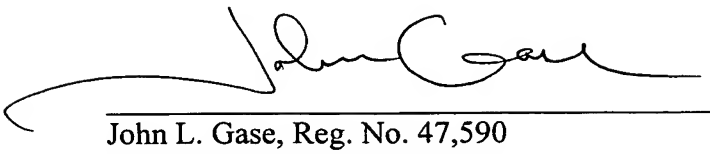
Discussion of the Objection to Embedded Hyperlinks

The Office objects to the specification due to the recitation of internet addresses that are considered by the Office to be hyperlinks or browser-executable code. The internet addresses have been removed from the specification and replaced with a description of the internet sites to which they refer. In view of this amendment, the objection is moot.

Conclusion

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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